Active Insulin and Nutrition Control for Tight Glycaemic Regulation in Critically Ill Patients

Xing-Wei WONG[1], J Geoffrey CHASE[3], Geoffrey M SHAW[2], Christopher E HANN[3], Thomas LOTZ[1], Jessica LIN[1], Ishan SINGH-LEVETT[1] and Laura J HOLLINGSWORTH[1]

[1] Department of Mechanical Engineering, University of Canterbury

[2] PhD, Department of Mechanical Engineering, University of Canterbury

[2] MbChB, FJFICM, Department of Intensive Care, Christchurch Hospital, Christchurch School of Medicine and Health Science, University of Otago

[3] PhD, Department of Mechanical Engineering, University of Canterbury, Christchurch School of Medicine and Health Science, University of Otago

Work performed at:
Department of Intensive Care, Christchurch Hospital
Department of Mechanical Engineering, University of Canterbury
Christchurch School of Medicine and Health Sciences, University of Otago

Address for Reprints: Reprints available from
Dr J. Geoffrey Chase
Department of Mechanical Engineering
University of Canterbury
Private Bag 4800
Christchurch
New Zealand
geoff.chase@canterbury.ac.nz

Financial Support:
University of Otago Internal Studentship Grant
Christchurch ICU Trust

Keywords:
Critical Care, Hyperglycemia, Retrospective Studies, ICU, Blood Glucose, Insulin

Abstract:

Stress-induced hyperglycaemia is prevalent in intensive care and tight glucose control can reduce mortality by up to 43%. This research develops an adaptive control algorithm varying insulin dose and nutritional inputs for targeted glucose control in critical care. Retrospective ICU patient data (n = 19) was used for simulated long-term glucose regulatory trials to validate the approach. A 312% increase in periods of normoglycaemia compared to retrospective patient data was recorded while feeding 20% greater nutrition. Two 10-hour proof-of-concept trials were also conducted in the Christchurch ICU. Overall mean target error was 8.7%. 61% of targets were achieved within ±5% and the two measurements with errors >20% were recorded during rapid change in patient condition. The absolute error range ([0, 2.9] mmol/L) indicates small errors at low glucose values. Overall, the protocol demonstrated effective glycaemic control across the patient cohort and varying patient condition, indicating that the absolute quantity of insulin and nutrition administered are less critical than their strategic delivery in maintaining tight glucose control.

1. INTRODUCTION

Critically ill patients often experience stress-induced hyperglycaemia and high insulin resistance, even with no prior diabetes (1-4). Increased secretion of counter-regulatory hormones lead to a rise in endogenously produced glucose, as well as a reduction in insulin sensitivity. Absolute and relative insulin deficiency, and drug therapy are added causes. Nutritional support regimes with high carbohydrate content also exacerbate hyperglycaemia by compounding the impact of the counter-regulatory response (3-6) with added enteral nutrition (7-9).

Although hyperglycaemia can be a marker of severity of illness, it also worsens outcomes, leading to an increased risk of further implications such as severe infection (10), myocardial infarction (1), and polyneuropathy and multiple-organ failure (2). van den Berghe (2, 11) showed that tight glucose control to less than 6.1mmol/L reduced cardiac ICU patient mortality by up to 45%, while Krinsley (12, 13) showed a 17-29% total reduction in mortality over a wider ICU population with a higher glucose limit of 7.75mmol/L.

Short-term, adaptive model-based protocols for insulin-mediated glucose control have been developed utilising integral-based identification of time-varying patient specific parameters (14, 15). These insulin-based protocols are suited for clinical use, but have limitations. More specifically, low insulin sensitivity due to the stress of condition and increased counter-regulatory dynamics can result in hyperglycaemia regardless of insulin infusion level (14, 15). The main reason for this result is that

insulin effect saturates at high insulin concentrations (15, 16), limiting the equilibrium blood glucose level that can be achieved if effective insulin resistance is very high.

As a result, if the impact of insulin is limited, the only other avenue to regulate blood glucose is to limit exogenous nutritional inputs exacerbating the problem. Research with low glucose nutrition in critical care has seen significant reductions in average blood glucose levels (7). Hence, reduced glucose nutrition combined with insulin administration can act to control both sides (input and removal) of the glucose balance.

This paper develops a robust controller for safe, predictable regulation of glucose levels under elevated insulin resistance. The algorithm developed accounts for variable external nutritional inputs while adapting to inter-patient variability and time-varying physiological condition. The protocol requires relatively infrequent glucose measurement to minimise labour and patient discomfort, and enable easier clinical uptake.

Previous blood glucose control research includes controlled insulin infusion trials by Hovorka et al. (17), Chee et al. (18), and Chase et al. (15, 19). Adaptive bolus-based control using insulin alone by Chase et al. (15) forms the basis of this work. The primary difference in this research is the improvement in control under elevated insulin resistance by modulating nutritional support in addition to insulin input.

2. METHODS

2.1 System model

Tight blood glucose control requires a patient-specific glucose-insulin regulatory system model that captures the fundamental dynamics. Chase et al. (14, 15) used an extended system model that captured rate of insulin utilisation, insulin losses and saturation dynamics, and is also used in this study:

$$\dot{G} = -p_G G - S_I (G + G_E) \frac{Q}{1 + \alpha_G Q} + P(t) \tag{1}$$

$$\dot{Q} = -kI + kQ \tag{2}$$

$$\dot{I} = -\frac{nI}{1 + \alpha_I I} + \frac{u_{ex}}{V} \tag{3}$$

where $G(t)$ [mmol/L] is the plasma glucose above an equilibrium level, G_E [mmol/L], and $I(t)$ [mmol/L] is the plasma insulin resulting from exogenous insulin input, $u_{ex}(t)$ [mU/min]. The effect of previously infused insulin being utilised over time is represented by $Q(t)$ [mU/L], with k [1/min] accounting for the effective life of insulin in the system. Patient endogenous glucose clearance and insulin sensitivity are p_G [1/min] and S_I [L/(mU.min)], respectively. The parameter V [L] is the insulin distribution volume and n [1/min] is the constant first order decay rate for insulin from plasma. Total plasma glucose input is denoted $P(t)$ [mmol/(L.min)]. Michaelis-Menten functions are used to model saturation, with α_I [L/mU] used for the saturation of plasma insulin disappearance, and α_G [L/mU] for the saturation of insulin-dependent glucose clearance (14, 15).

For simulations performed in this study, k, n, α_G, α_I and V were set to generic population values (15, 20). For the clinical trials, k, α_G and V can be tuned to match the patient's dynamics, while the glucose distribution volume was taken as 0.19L/kg of the patient total body mass (21-23).

The parameters n and α_I were set to 0.16min^{-1} and 0.0017L/mU (15), which is consistent across many studies e.g. (24-27). The parameter α_G = 1/65L/mU is an initial conservative choice for more likely underestimation of saturation (15, 16, 28). Finally, $k = 0.0198\text{min}^{-1}$ gives an effective insulin half-life of 35min (15).

In Equation (1), G_E represents the patient-specific equilibrium state under constant feed, insulin infusion, insulin sensitivity and glucose clearance. However, an instantaneous equilibrium blood glucose level can be difficult to determine (14). Hence, the current glucose value is used to update G_E every two hours after a feed rate modulation.

Equation (3) does not include endogenous insulin production. Critically ill patients are also often hyperinsulinaemic. Although endogenous insulin production is quite consistent across the non-critically ill population (17, 26, 29, 30), its value can be highly variable and difficult to obtain quickly in critical care. Failing to model endogenous insulin production can lead to low modelled insulin sensitivity, S_I, resulting in a large insulin dose prescribed. However, endogenous insulin production is also suppressed by significant exogenous insulin administration (23, 26, 31). Hence, in this study, an unknown, steady endogenous insulin supply is assumed and its effect is included in the time-varying parameter p_G.

2.2 Variable enteral nutrition model

Chase et al. (15) modelled the constant enteral feed rate, *P(t)*, in their trials as a constant value. In this study, non-steady stepwise enteral glucose fluxes are employed for control and modelled using exponential functions.

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (\overline{P}_i - \overline{P}_{i+1})e^{-k_{pd}(t-t_i)} \text{ where } \overline{P}_{i+1} < \overline{P}_i \quad (4)$$

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (\overline{P}_i - \overline{P}_{i+1})e^{-k_{pr}(t-t_i)} \text{ where } \overline{P}_{i+1} > \overline{P}_i \quad (5)$$

where k_{pr} and k_{pd} (1/min) are the effective half lives of glucose transport from gut to plasma for both increasing (k_{pr}) and decreasing (k_{pd}) feed rates, and $\overline{P}_1$ and $\overline{P}_2$ are the steps in enteral glucose feed rates.

Many studies have investigated glucose kinetics under non-steady conditions using tracers. Post-prandial glucose kinetics are characterised by suppression of hepatic glucose output for both an oral glucose load (OGL) and continuous feeding approach (21, 32, 33). Glucose disposal rate is largely unaffected (21, 32, 34). Time periods for complete glucose absorption range from 120 to 240min (33-36) for an OGL with the peak in total glucose rate of appearance (GRa) arriving in ~40mins (~$t_{1/2}$ of 20mins) (33). Slower absorption was evidenced in a mixed meal formulation (37), and (21) showed that mixed-meal post-prandial GRa increased progressively until near steady-state between 230 and 270 minutes.

A high percentage of oral glucose passes through the liver and appears systemically (92%±2%, (33)), only sustaining an 8% first-pass splanchnic uptake. Rapid intestinal absorption results in a very quick rise in total GRa while low hepatic trapping by the liver results in a total GRa curve that is very similar to the oral GRa curve (33). Together with a suppression of endogenous glucose production (~50% in non-diabetic subjects, (38, 39) and up to 91% in diabetics, (32, 33, 39)) the total glucose appearance consists almost entirely of oral glucose (33). Whether such dynamics are applicable to non-steady-state enteral glucose infusions where variations in glucose load are much smaller is unknown, although (33) showed no discernible difference in systemic oral glucose appearances with a half-sized oral glucose load.

Model-based methods of calculating glucose fluxes (33, 40, 41) using tracer concentrations are unsuitable for real-time clinical application. Hence, different exponential rates for total GRa rise (k_{pr}) and decay (k_{pd}) can be used to model transient hepatic glucose output and first-pass splanchnic uptake in non-steady feeding. Impaired suppression of basal hepatic glucose output in diabetes and stress-induced hyperglycaemia (21, 42) imply a slow decay rate in total GRa following nutritional feed reduction. Conversely, a low first-pass splanchnic uptake, resulting in increased systemic glucose appearance implies a rapid rise rate in total GRa. Therefore, the values of k_{pr} and k_{pd} are set to 0.0347min^{-1} and 0.0068min^{-1} from data in the literature, corresponding to half-lives of 20 and 100mins.

Figure 1 shows modelled nutritional input, $P(t)$, following enteral feed rate variations using $k_{pr} = 0.0347\text{min}^{-1}$ and $k_{pd} = 0.0068\text{min}^{-1}$. Note that this model only captures the

first order dynamics of glucose appearance as a function of enteral feed. Hence, Equations (4)-(5) effectively assume a linear, 2-compartment model.

3. FITTING METHOD AND CONTROL ALGORITHM

The controller sets hourly blood glucose level targets. Targets are achieved by a combination of insulin bolus, insulin infusion and/or modulating the nutritional feed rate. The goal is to regulate blood glucose in the 4-6mmol/L band with a target of 5mmol/L.

Prior to resolving a bolus size and feed rate to achieve a target, S_I must be fitted. The parameter fitting is described in (14, 15). The main difference is the assumption of p_G = 0.01, a value found in (14) to be relatively constant and insensitive across a sampled ICU patient cohort. The fitted insulin sensitivity, S_I, is used to predict the blood glucose response in the following hour. The insulin sensitivity in the following hour ($\overline{S}_{\mathrm{I}_{(i+1)}}$) is estimated as a function of previously fitted insulin sensitivity values.

$$\overline{S}_{\mathrm{I}(i+1)} = \left\{ \begin{array}{ll} \dfrac{1}{11}\left\{8\left(\dfrac{\overline{S}_{\mathrm{I}_{i0}} + \overline{S}_{\mathrm{I}_{i1}}}{2}\right) + 2\left(\dfrac{\overline{S}_{\mathrm{I}_{(i-1)0}} + \overline{S}_{\mathrm{I}_{(i-1)1}}}{2}\right) + \left(\dfrac{\overline{S}_{\mathrm{I}_{(i-2)0}} + \overline{S}_{\mathrm{I}_{(i-2)1}}}{2}\right)\right\} & \mathrm{i} > 2 \\ \dfrac{1}{6}\left\{4\left(\dfrac{\overline{S}_{\mathrm{I}_{i0}} + \overline{S}_{\mathrm{I}_{i1}}}{2}\right) + 2\left(\dfrac{\overline{S}_{\mathrm{I}_{(i-1)0}} + \overline{S}_{\mathrm{I}_{(i-1)1}}}{2}\right)\right\} & \mathrm{i} = 2 \\ \dfrac{\overline{S}_{\mathrm{I}_{i0}} + \overline{S}_{\mathrm{I}_{i1}}}{2} & \mathrm{i} = 1 \end{array} \right\} \quad (6)$$

where the terms $\overline{S}_{\mathrm{I}_j}$ are defined in Figure 2, and i=1, 2, … is the number of prior hours of fitted insulin sensitivity values available. The average value (i=1) is obtained using the first two values, $\overline{S}_{\mathrm{I}_{i0}}$ and $\overline{S}_{\mathrm{I}_{i1}}$ fitted from 0 to 60 minutes after the first hour of the trial. In subsequent hours, a weighted average of prior fitted values is used to minimise the effect of outliers and/or erroneous glucose measurements on the fitted insulin sensitivity.

The required combination of bolus size, insulin infusion rate and/or nutritional feed rate to achieve the target glucose level is then determined iteratively using the estimated S_I value, and Equations (1)-(3). Delta functions are used to model insulin boluses, $u_{ex}(t)$, in Equations (1)-(3) with the duration of each bolus set to 1 minute. Similarly, Equation (4) is used to determine $P(t)$ based on hourly commanded step changes in nutritional input rate.

4. CLINICAL AND VIRTUAL TRIAL METHODOLOGY

Virtual trials are simulations using retrospective patient S_I *and* p_G from (20) to test the model and methods. Two sets of trials are run to test the control methods. Proof-of-concept clinical trials are then performed to confirm the basic results clinically. Both trials use the same control protocol and the clinical trials are described first.

4.1 Clinical trials

The proof-of-concept clinical trials span 10h. All patients were on a constant naso-gastric feed of RESOURCE™ Diabetic (Novartis Medical Nutrition, USA) at a rate

not exceeding 700 kilocalories of glucose per day (~80ml/hr), and given infusions of Actrapid™ (Novo Nordisk Pharmaceuticals Ltd., NZ). At the end of each hour, a 10-15% reduction in current blood glucose level is set as the target, depending on the estimated insulin saturation level (15). The minimum target level is 5mmol/L. Ethical consent was obtained from the Canterbury Ethics Committee.

Selected patients had the following inclusion criteria: *in situ* naso-gastric or other enteral feeding tube; tolerant of the maximal desired feeding rate as determined by the treating clinician; random glucose level >8mmol/L; and age >16 years. Exclusion criteria included: delayed gastric emptying (high residual 3-hourly gastric aspirates (>200ml); moribund or not expected to survive >72 hours; patients receiving neuromuscular blockade; and morbid obesity (BMI>35kgm^{-2}).

All patients were supine or semi-supine during the trial. Insulin was administered via an intravenous cannula with a Graseby 3500 syringe pump (Graseby Medical Limited, Colonial Way, Watford, Herts, WD24 4LG, UK). Enteral feed rate was maintained and manually controlled with a Ross Products Patrol Enteral Pump (Abbott Laboratories, Abbott Park, Illinois, U.S.A.).

4.2 Clinical trial procedure

The pre-trial period begins at 0600h, at which time the insulin infusion and feed rate are kept constant. Glucose readings are taken hourly to determine the patients' equilibrium blood glucose value, G_E. At 0900h, the feed rate is decreased by up to 30-40% depending on glucose level. Plasma glucose is then measured at 15min

intervals until 1000h. Paired blood samples are taken and analysed using a bedside Glucocard™ Test Strip II glucose testing kit (43).

Insulin sensitivity, S_I, is then fitted to the first hour of data. Using Equation (6), S_I is predicted for the next hour. A combination of insulin bolus size, insulin infusion rate, and enteral feed rate is resolved to achieve the target glucose value at the end of the next hour. Blood glucose is monitored every 30mins, and S_I re-evaluated every hour using the prior hours' data. Following each re-evaluation, the controller determines the required combination of control inputs to achieve the targeted glucose reduction as in the first hour. Hence, the overall approach is target-driven and incorporates real-time optimisation of insulin sensitivity for adaptive control. The overall clinical trial procedure is outlined in Figure 3.

A limit of 6U/hr is placed on the total insulin prescribed per hour. In addition, a 30mU/L cap was placed on the estimated ineffective insulin, defined by the model as the estimated interstitial insulin, Q minus the effective, saturated insulin, $\overline{Q}$ where $\overline{Q} = \frac{Q}{1+\alpha_G Q}$ (15). Glucose feed rate was limited to between 280kcal/day and the newly imposed standard of 700kcal/day for this ICU. At the 280kcal/day minimum, the total caloric intake is still 778kcal/day (44), which exceeds the level found to avoid an increased risk of bloodstream infections (45).

4.3 Virtual trial patient cohort

Long-term virtual trials were performed using data from a random selection of 17 patients from a 201 patient data audit at Christchurch Hospital (14, 20). Retrospective

data from 2 clinical trial patients prior to their participation was also included for a total of 19 patients. Each record had a period exceeding 1 day with intervals between glucose measurements of 3h or less, giving adequate data density for accurate model fitting. The average length of the data was 3.9 days with a range of 1.4-18.8 days. A bias towards diabetics is due to the 3h data density required, as diagnosed diabetics were more closely monitored from admission. This cohort represents a general cross-section of ICU population, in medical subgroup, APACHE II score, age, sex and mortality (see Table 1). Ethical consent was granted by the Canterbury Ethics Committee for this retrospective analysis.

4.4 Virtual trial simulation procedure

The virtual trial simulations were performed using identified patient specific parameter (p_G and S_I) profiles fitted to the retrospective blood glucose patient data from (14). Using identified $p_G(t)$ and $S_I(t)$ profiles simulates a physiological patient response or 'virtual patient' with the assumption that the parameters are independent of the control inputs administered. Hence, a virtual patient response can be created for any glucose or insulin inputs. The virtual trials were performed using an identical control protocol as the clinical trials but over the entire length of data available. The virtual trials aim to determine the long-term efficacy of the control protocol compared to 'hospital control' in the Christchurch ICU using actual retrospective hospital data as well as an insulin-only control protocol (15).

Each hour, the controller fits a value of S_I to the blood glucose measurements received from the 'virtual patient', which it then uses, via Equation (6), to predict the patient response based on its calculated control inputs. The control inputs are then run on the

'virtual patient' to generate the 'actual' response based on the known patient parameter profile. A normally distributed error of ±7% is added to the measured glucose values to simulate the sensor error of the Glucocard™ Test Strip II used clinically.

A constant enteral feed rate of 1000kcal/day of glucose was used for the insulin-only control protocol of (15). For the variable feed and insulin control protocol, the initial feed rate was taken to be the standard glucose 1000kcal/day and the imposed permissible range of variation was 280-1000kcal/day of glucose. The higher standard feed rate is used as it was standard for the retrospective patients in this cohort.

Note that many feed rate variations that occur in intensive care are not explicitly intended for maintaining euglycaemia and the initial actual patient feed rate may differ from the constant 1000kcal/day rate assumed. Thus, especially initially, the retrospective patient glucose curve may not be directly comparable with the curves of the other two control protocols. However, the feed rates would only have been reduced in hospital from this value, so the comparison to a constant 1000kcal/day value under the two protocols is conservative and favours the recorded retrospective patient data.

5. VIRTUAL TRIAL RESULTS AND DISCUSSION

Two of the 19 virtual trial results are shown. Figure 4 shows the results for Patient 87 for hospital control captured directly from the retrospective data, insulin-only control from (15), and variable feed and insulin control. Tight glucose control in the 4-

6mmol/L normal band for this patient with the control protocol developed is clear compared to both the insulin-only and hospital protocols. The total amount of insulin administered by the variable feed and insulin protocol was 38.5% less than the insulin-only protocol (410.5U versus 667.0U). From the retrospective patient data, the total insulin infused was 248.0U, indicating another source of poor control. Time spent in the desired 4-6mol/L band was 89% versus 21.8% for the insulin-only protocol and 10.7% for hospital control. The result for the protocol developed was achieved with identical total enteral glucose administered to the retrospective patient data (1284g versus 1286g).

Compared to the insulin-only protocol, which held the feed rate constant, the variable feed and insulin protocol modulated both control inputs as driven by the estimated effective insulin sensitivity, as seen in Figure 5. During periods of high insulin sensitivity, less insulin was required and consequently prescribed, while the standard feed rate was maintained. When the identified insulin sensitivity decreased significantly, the feed rate was reduced and insulin administered increased to maintain blood glucose in the desired band. This result shows that the controller recognizes, and can compensate for, periods where patient condition precludes adequate control with insulin alone.

The increase in blood glucose level between 2500 and 4500mins in Figure 4 with the insulin-only protocol corresponds to a period of very low insulin sensitivity in Figure 5. With no feed rate reduction possible, increased insulin resistance resulted in the glucose equilibrium level rising to its maximum value of 17.3mmol/L, even though the insulin administered was identical to other periods in the simulation.

In the first 4500mins, hospital control appears more effective than the insulin-only protocol because of the lower hospital feed rate in Figure 5, not more efficient insulin prescription. This result is a case where the insulin-only protocol comparison to hospital control is conservative. Glucose levels were normal in the 4-6mmol/L band under hospital control only during periods of minimum feed rate between 1600 and 2800mins. This last result further implies that feed rate reduction is the only alternative to maintain euglycaemia under these typical high insulin resistance levels.

For Patient 2 in Figure 6, both the developed and insulin-only protocols were unable to restrain the glucose level when the insulin sensitivity decreased significantly in the first 250mins of the simulation. With the assumed decay rate ($t_{1/2}$ = 100mins) in total GRa, glucose is modelled as still entering the plasma from its assumed 1000kcal/day initial value, even though the feed rate was reduced to minimum at 0mins. Hence, these protocols failed initially to control the glucose level, as seen in Figure 6.

Note that assuming the initial 1000kcal/day feed rate for the two control protocols resulted in their curves not being directly comparable to the hospital control curve, which starts with zero feed for 1260mins. Hospital control was only able to maintain the lower glucose levels in this period by fasting the patient, as seen in Figure 7. However, this choice was not made to control glucose specifically, but for other clinical reasons which typically include increased gastric residual volumes, vomiting, bowel perforation, and for medical procedures.

The total insulin administered according to hospital data was 213.0U due to the initial fasting period. The insulin-only protocol prescribed 486.1U and the variable feed rate

and insulin protocol, 369.8U, 23.9% less. The variable insulin and feed protocol delivered 931g of glucose versus 672g from the retrospective patient data, an increase of ~40%. Despite the 'disadvantage' of greater feed, the protocol developed achieved a higher 78.4% time-in-band versus 3.6% for hospital protocol and 0.9% for the insulin-only protocol.

Hospital control is more effective than the insulin-only protocol for Patient 2 because of the 27.5% lower hospital feeding and is another case where the insulin-only protocol comparison to hospital control is conservative. The outcome of the insulin-only protocol is further compounded by the lower mean insulin sensitivity of Patient 2. Even with a higher feeding rate, the insulin-only protocol performed better overall for Patient 87 who had higher mean insulin sensitivity. For Patient 2, the insulin-only protocol obtained a mean glucose level of 9.8mmol/L compared to 7.8mmol/L from the retrospective patient data. This result strengthens the idea that feed reduction is more effective at controlling blood glucose under the low insulin sensitivity typically encountered in hyperglycaemic critical care patients.

For Patient 87, the variable feed and insulin controller significantly increased the time spent in the 4-6mmol/L band by 4.1 times and 8.3 times over the insulin-only and hospital protocols respectively. For Patient 2, whose mean insulin sensitivity was 25.3% lower than Patient 87, the results are 87.1 times and 21.8 times respectively.

5.1 Summary of all virtual trial simulations

A summary of the results for all 19 patients is shown in Table 2. Overall, the variable feed and insulin controller increased the time spent in the 4-6mmol/L band by 240%

compared to the insulin-only protocol and 312% versus the patient data. Time spent above the 4-6mmol/L band was reduced by 231% and 237% respectively.

Table 3 shows the glucose and insulin administered with the protocol developed here as compared to retrospective patient data, and the insulin-only protocol. On average, the total amount of insulin prescribed by the developed protocol was 33% less than the insulin-only protocol and 1.6 times more than retrospective patient data. The efficiency of the developed protocol is further revealed in the total glucose administered, which exceeded the retrospective patient data by 19.5% on average. The developed protocol was feeding an average of 718kcal/day compared to the 634kcal/day by the hospital protocol, which also had greater variability. Hence, the better control was obtained with 60% more insulin and 20% more feed. This last result also indicates that it is the strategic timing of insulin and nutritional input deliveries more than their average level that determines tightness of control.

Figure 8 summarises these results by plotting percentage time in the 4-6mmol/L band versus the log mean S_I on the x-axis. The general trend, as illustrated by Patients 2 and 87, is that percentage time-in-band and mean blood glucose level decreases with all protocols with decreasing mean insulin sensitivity. With insulin alone, performance is highly dependent on the patients' effective insulin resistance (Table 4). The variable feed rate and insulin protocol provided tighter blood glucose control across the range of insulin sensitivities and significantly higher time-in-band. The insulin-only protocol only reached similar levels of high glucose control at high insulin sensitivities, and even then, with significantly larger amounts of administered insulin. For hospital control, greater variation in blood glucose control was recorded,

as expected (R=0.4877, p<0.04), and showed tighter control than the insulin-only protocol only at low insulin sensitivities, where clinically selected feed reductions affected the comparison, as with Patient 2.

It is important to note that most, or all, of the clinical, hospital reductions in feed rate were not performed for hyperglycaemia. Similarly, the insulin-only protocol had a conservative 1000kcal/day constant feed rate to manage, showing more efficient insulin delivery than hospital control despite this handicap. Considering the recently imposed 700kcal/day glucose nutrition limit at Christchurch Hospital, improvements would be seen in the insulin-only protocol results.

6. CLINICAL PROOF-OF-CONCEPT TRIALS

This section presents two out of an ongoing series of clinical trials of the variable feed and insulin control protocol. The goal is to demonstrate the basic results seen in simulation and prove the concept.

6.1 Trial A

Patient A was a 64-year-old male, admitted into intensive care post-operatively following a bypass operation, and suffering from sepsis and acute renal failure. It was his 6th day of stay in the ICU and his equilibrium blood glucose level was 8.7mmol/L at the start of the trial. The initial assumed value of k = 0.0198 min^{-1} corresponding to a half-life of 35mins resulted in a smooth, fitted insulin sensitivity parameter, S_I for most of the trial and thus, did not require further modification. The k_{pd} value of 0.0068 min^{-1} also matched observed patient dynamics without further adaptation.

The trial progression and modelled patient dynamics are shown in Figure 9 and Table 5. The feed rate was reduced from 700 to 420kcal/day in the first hour but was increased to 670kcal/day at 120mins to counter the rate of decrease in glucose level. Subsequent feed rate reductions were prescribed at 180mins to 520kcal/day and to the 280kcal/day minimum at 240mins, which was held until trial completion. The insulin boluses required grew larger after 180mins, as seen in the second panel.

From 0 to 120mins, the insulin sensitivity fitted was relatively high and required little insulin or feed reduction to obtain a lower glucose level. At 150mins, the glucose measurement was on course for the 180min target of ~5mmol/L. The measurement of 8.5mmol/L at 180min is not fully explainable, but is due to a sudden change in patient condition. The most likely cause is the serious episode of arrhythmia the patient suffered around that time, which highlights how the stress of condition in the critically ill promotes the counter-regulatory response and sudden changes in insulin resistance and glucose levels.

Although three targets were missed at 120, 180 and 240mins, the model simulation was tracking the blood glucose measurements accurately within the next hour and the target at 300mins was achieved (5.1% error). Target acquisition was then maintained for the remainder of the trial as the insulin sensitivity remained reasonably constant, resulting in a less than 1mmol/L absolute error. However, insulin sensitivity remained low and large feed rate reductions and insulin boluses were required to achieve good control.

Table 5 shows the target errors in percentage and absolute value. The mean error in target acquisition was 15.1% (range: 0-54.1%). Without the large error at 180mins as patient condition changed suddenly, the average error was 10.2%, which is near the 7-12% measurement error for these glucose ranges (43). The average absolute error of 0.68mmol/L, or 0.92mmol/L including the error at 180mins, shows the relatively minor blood glucose errors involved in maintaining tight control at this level.

The reduction in blood glucose was 34.9% from the initial moderately hyperglycaemic 8.7mmol/L to a final value of 6.45mmol/L. Due to high insulin resistance, even with the imposed limit of 6U/hr of insulin, the glucose level was irreducible at that time and remained above 6mmol/L. However, this trial demonstrates the control algorithms ability to maintain a controlled reduction in glucose level and adapt quickly to rapidly changing patient condition.

6.2 Trial B

Patient B was a 73-year old, insulin dependent Type II diabetic male admitted into ICU with aspiration pneumonia secondary to mediastinal sepsis and an oesophagectomy. The patient had spent 29 days in ICU, and the equilibrium glucose level at the start of the trial period was 6.8mmol/L, although he had significantly elevated blood glucose levels (9-10mmol/L) earlier. With near normal initial blood glucose, the controller would be trialled in maintaining tight control throughout the 10-hour trial period, which would not be possible if the initial blood glucose level was hyperglycaemic (as in Patient A). The results are shown in Figure 10 and Table 6.

Patient B had a body weight of 100kg, which was used to estimate the glucose distribution volume, V = 19L. The standard values of α_G = 1/65 L/mU, k = 0.0198 (half-life of 35mins), k_{pd} = 0.0068 min^{-1} (half-life of 100min) and k_{pr} = 0.0347 min^{-1} (half-life of 20min) were used. The resulting fitted insulin sensitivity was very smooth with only minor discontinuities between each fit, indicating that the assumed parameter values were close to their actual values.

The insulin infusion was kept constant throughout the trial at the initial value of 1.5U/hr, except for a one hour period, and supplemented with six boluses of 0.5-1.5U. The feed rate was reduced from 550-365kcal/day for the first four hours and up to 464kcal/day by the end of the trial. For the first 5 hours, the blood glucose was reduced and then held at 5mmol/L.

The rise in blood glucose between 300mins and 480mins was caused by a clinical miscommunication. The control input at 300mins as determined by the controller was to maintain the insulin infusion at 1.5U/hr and administer a 0.6U insulin bolus, but was misconstrued by the attending nurse as reduce the insulin infusion to 0.6U/hr only. The resultant increase in blood glucose was halted at 420mins into the trial when the controller was finally given the correct values. Even so, the controller predicted the rise in glucose accurately when the data was updated.

The mean target error was 2.3% (range: 0-5%) and a maximum absolute error of 0.25mmol/L was recorded. The insulin sensitivity distribution for the whole trial remained relatively constant, which contributed to the high rate of successful target acquisition. Overall, the errors were very low and all targets were met.

The reduction in blood glucose achieved was 30.1% from the initial mild hyperglycaemia of 6.8mmol/L to a final value of 4.75mmol/L. With significantly higher insulin sensitivity compared to Patient A, the glucose level was reduced and maintained in the 4-6mmol/L target band with insulin only, without resorting to a large feed rate reduction. This trial also demonstrates the control algorithms' ability to maintain a controlled reduction in glucose level while using the maximum feed rate possible, given the patients' higher fitted insulin sensitivity.

6.3 Target acquisition error summary

The overall mean target error for both clinical trials was 8.7% (0.5mmol/L), with an absolute range of [0, 2.9]mmol/L. The Glucocard™ Test Strip II bedside glucose monitoring sensor is capable of obtaining 50% of measurements within ±5% error and 98% within ±20% over the typical glucose range (46). Across both clinical trials, 61% of the targets were achieved within ±5% with a mean target error of 2.3% (0.1mmol/L). Mean target error for errors >5% was 18.8% (1.2mmol/L). Out of the 18 targets, only two had errors larger than 20% so that 89% of all measurements were within ±20% of targets. The target errors obtained are thus explainable by the published measurement errors from literature. More data from ongoing trials will confirm whether current target errors are within reported sensor parameters or partly due to other systematic problems. The maximum target error was 54.1% obtained in Trial A during a rapid change in patient condition as discussed previously.

7. CONCLUSIONS

Both the long-term virtual trial simulations and clinical trials conducted demonstrated the potential of a control algorithm modulating both insulin and nutritional feed rate to accurately reduce and tightly regulate glucose levels despite significant inter-patient variability and time-varying physiological condition. A simple, two-compartment model for enteral feed rate was also presented.

Simulated trials conducted across a wide ICU population cross-section showed that glucose management with long-term intensive insulin therapy and feed rate modulation resulted not only in a reduction in absolute glucose levels but in the severity of fluctuation in glucose values. A 312% mean increase in time spent in the desired 4-6mmol/L band was achieved compared to using a constant feed rate and the same insulin control. More importantly, a mean reduction of 237% in time spent over the 4-6mmol/L band at hyperglycaemic blood glucose levels was obtained compared to the retrospective data. Furthermore, the results were achieved with only 60% more insulin administered and a 20% increase in enteral glucose nutrition compared to the retrospective patient data. These results demonstrate that the absolute amounts of insulin and glucose feed administered are less crucial in the tight regulation of glucose levels than an outcomes-based continuous protocol whose advantage is garnered with the minimum control effort and hence dose of insulin required, while still providing maximal feeding to the patient.

The efficacy of the adaptive control algorithm and system model presented in achieving targeted control in critically ill patients was validated in two proof-of-

concept clinical trials. The results showed both accurate regulated stepwise glycaemic reduction and tight glycaemic maintenance, with an average hourly target error across the two patients of 8.7% with 61% of errors within ±5% and 89% within ±20%. Two measurements had target errors exceeding 20% and were attributable to periods where the controller was adapting to sudden changes in patient condition. The target errors were consistent with and explainable by the published sensor error distributions. Notably, the average error was less than 0.8mmol/L, a small value compared to the 4-6mmol/L desired.

A larger patient cohort will be tested to further analyse its effectiveness and improve its performance. Trials spanning longer periods of time are also in development to verify the long-term trial simulations performed and to test the adaptability of the controller. Clinically, these results indicate the potential in both simulation and shorter clinical trials to reduce ICU mortality.

REFERENCES

(1) Capes, S. E., Hunt, D., Malmberg, K., and Gerstein, H. C., Lancet, Vol. 355, No. 9206 (2000), p. 773-778.

(2) Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M., Vlasselaers, D., Ferdinande, P., Lauwers, P. , and Bouillon, R., N Engl J Med, Vol. 345, No. 19 (2001), p. 1359-1367.

(3) Mizock, B. A., Best Pract Res Clin Endocrinol Metab, Vol. 15, No. 4 (2001), p. 533-51.

(4) McCowen, K. C., Malhotra, A. , and Bistrian, B. R., Crit Care Clin, Vol. 17, No. 1 (2001), p. 107-24.

(5) Thorburn, A., Litchfield, A., Fabris, S., and Proietto, J., Diabetes Research and Clinical Practice, Vol. 28, No. 2 (1995), p. 127-135.

(6) Larsen, M. O., Rolin, B., Wilken, M., Carr, R. D., and Svendsen, O., Vol. 967 (2002), p. 414-423.

(7) Patino, J. F., de Pimiento, S. E., Vergara, A., Savino, P., Rodriguez, M. , and Escallon, J., World J Surg, Vol. 23, No. 6 (1999), p. 553-9.

(8) Weissman, C., Crit Care, Vol. 3, No. 5 (1999), p. R67-75.

(9) Woolfson, A. M., Intensive Care Med, Vol. 7, No. 1 (1980), p. 11-4.

(10) Bistrian, B. R., JPEN J Parenter Enteral Nutr, Vol. 25, No. 4 (2001), p. 180-181.

(11) Van den Berghe, G., Wouters, P. J., Bouillon, R., Weekers, F., Verwaest, C., Schetz, M., Vlasselaers, D., Ferdinande, P. , and Lauwers, P., Crit Care Med, Vol. 31, No. 2 (2003), p. 359-366.

(12) Krinsley, J. S., Crit Care Med, Vol. 31 (2003), p. A19.

(13) Krinsley, J. S., Mayo Clin Proc, Vol. 79, No. 8 (2004), p. 992-1000.

(14) Hann, C. E., Chase, J. G., Lin, J., Lotz, T., Doran, C. V. , and Shaw, G. M., Comput Methods Programs Biomed, Vol. 77, No. 3 (2005), p. 259-70.

(15) Chase, J. G., Shaw, G. M., Lin, J., Doran, C. V., Hann, C., Robertson, M. B., Browne, P. M., Lotz, T., Wake, G. C. , and Broughton, B., Med Eng Phys, Vol. 27, No. 1 (2005), p. 1-11.

(16) Prigeon, R. L., Roder, M. E., Porte, D., Jr., and Kahn, S. E., J Clin Invest, Vol. 97, No. 2 (1996), p. 501-507.

(17) Hovorka, R., Shojaee-Moradie, F., Carroll, P. V., Chassin, L. J., Gowrie, I. J., Jackson, N. C., Tudor, R. S., Umpleby, A. M. , and Jones, R. H., Am J Physiol Endocrinol Metab, Vol. 282, No. 5 (2002), p. E992-1007.

(18) Chee, F., Fernando, T. , and van Heerden, P. V., Anaesth Intensive Care, Vol. 30, No. 3 (2002), p. 295-307.

(19) Doran, C. V., Hudson, N. H., Moorhead, K. T., Chase, J. G., Shaw, G. M. , and Hann, C. E., Medical Engineering & Physics, Vol. 26, No. 10 (2004), p. 855-866.

(20) Doran, C. V., University of Canterbury (2004).

(21) Kiwanuka, E., Barazzoni, R., and Tessari, P., Diabetes Nutrition & Metabolism, Vol. 14, No. 6 (2001), p. 315-324.

(22) Wolfe, R. R., Principles and practice of kinetic analysis (1992), p. 119-144.

(23) DeFronzo, R. A., Tobin, J. D., and Andres, R., Am J Physiol, Vol. 237, No. 3 (1979), p. E214-23.

(24) Thorsteinsson, B., Fugleberg, S., Feldt-Rasmussen, B., Ellemann, K., and Binder, C., Pharmacol Toxicol, Vol. 60, No. 2 (1987), p. 90-95.

(25) Bergman, R. N., Phillips, L. S., and Cobelli, C., J Clin Invest, Vol. 68, No. 6 (1981), p. 1456-1467.

(26) Ellemann, K., Thorsteinsson, B., Fugleberg, S., Feldt-Rasmussen, B., Andersen, O. O., Gronbaek, P. , and Binder, C., Clin Endocrinol (Oxf), Vol. 26, No. 5 (1987), p. 623-628.

(27) Kuehn, L., and Blundell, T., John Wiley and Sons (1980), p. 185-196.

(28) Rizza, R. A., Mandarino, L. J., and Gerich, J. E., Am J Physiol, Vol. 240, No. 6 (1981), p. E630-639.

(29) Bergman, R. N., Finegood, D. T., and Ader, M., Endocr Rev, Vol. 6, No. 1 (1985), p. 45-86.

(30) Furler, S. M., Kraegen, E. W., Smallwood, R. H. , and Chisholm, D. J., Diabetes Care, Vol. 8, No. 6 (1985), p. 553-561.

(31) Transberg, K., Hagander, P., and Thorell, J., Acta Endocrinol (Copenh), Vol. 97 (1981), p. 391-397.

(32) Ludvik, B., Nolan, J. J., Roberts, A., Baloga, J., Joyce, M., Bell, J. M., and Olefsky, J. M., Journal of Clinical Investigation, Vol. 100, No. 9 (1997), p. 2354-2361.

(33) Radziuk, J., McDonald, T. J., Rubenstein, D., and Dupre, J., Metabolism-Clinical and Experimental, Vol. 27, No. 6 (1978), p. 657-669.

(34) Ludvik, B., Nolan, J. J., Roberts, A., Baloga, J., Joyce, M., Bell, J. M. , and Olefsky, J. M., Journal of Clinical Investigation, Vol. 95, No. 5 (1995), p. 2232-2238.

(35) Cummins, A. J., J. Clin. Invest., Vol. 31 (1952), p. 928-937.

(36) Consoli, A., Diabetes Care, Vol. 15, No. 3 (1992), p. 430-441.

(37) Pehling, G., Tessari, P., Gerich, J. E., Haymond, M. W., Service, F. J. , and Rizza, R. A., Journal of Clinical Investigation, Vol. 74, No. 3 (1984), p. 985-991.

(38) Ferrannini, E., Simonson, D. C., Katz, L. D., Reichard, G., Bevilacqua, S., Barrett, E. J., Olsson, M., and Defronzo, R. A., Metabolism-Clinical and Experimental, Vol. 37, No. 1 (1988), p. 79-85.

(39) Mitrakou, A., Kelley, D., Veneman, T., Jenssen, T., Pangburn, T., Reilly, J. , and Gerich, J., Diabetes, Vol. 39, No. 11 (1990), p. 1381-1390.

(40) Mari, A., Stojanovska, L., Proietto, J. , and Thorburn, A. W., Computer Methods and Programs in Biomedicine, Vol. 71, No. 3 (2003), p. 269-281.

(41) Steele, R., Ann. N. Y. Acad. Sci., Vol. 82 (1959), p. 420-430.

(42) Firth, R., Bell, P., Marsh, H., Hansel, I., and Rizza, R., J. Clin. Invest., Vol. 74 (1985), p. 1525-1532.

(43) Arkray, Arkray Inc. (2001).

(44) Novartis, Novartis Medical Nutrition (2005).

(45) Rubinson, L., Diette, G. B., Song, X., Brower, R. G. , and Krishnan, J. A., Crit Care Med, Vol. 32, No. 2 (2004), p. 350-7.

(46) Weitgasser, R., Gappmayer, B., and Pichler, M., Clinical Chemistry, Vol. 45, No. 10 (1999), p. 1821-1825.

FIGURES

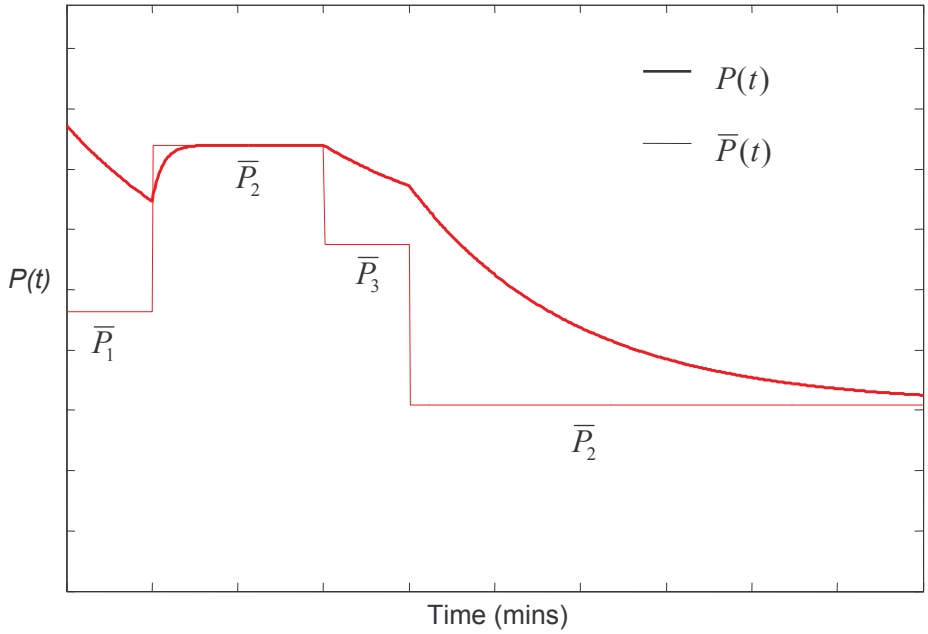

Figure 1: Stepwise nutritional variation and modelled total plasma nutritional input, *P(t)*

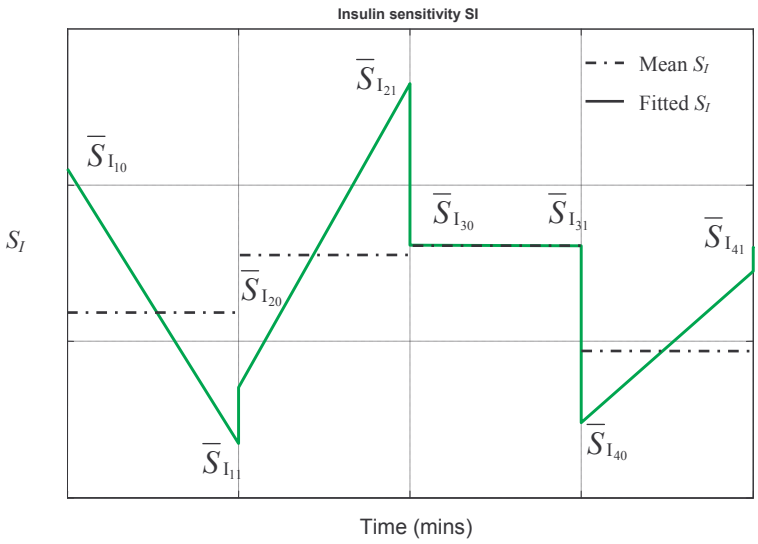

Figure 2: Fitted insulin sensitivity values

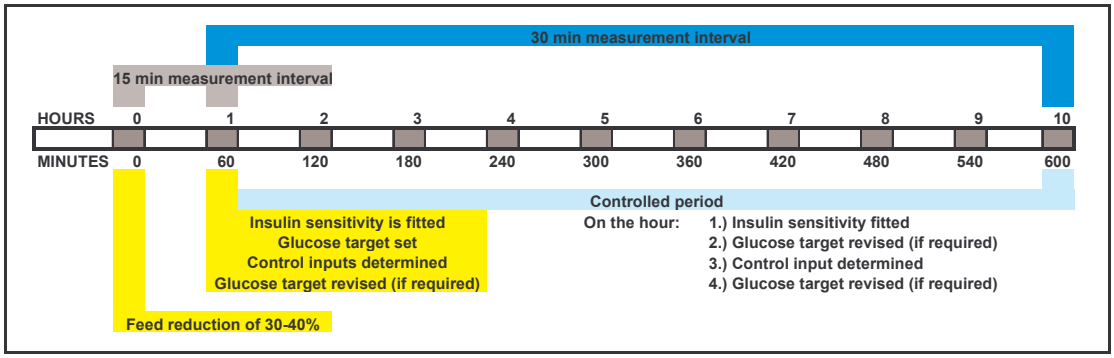

Figure 3: 10-hour clinical trial procedure from 0900

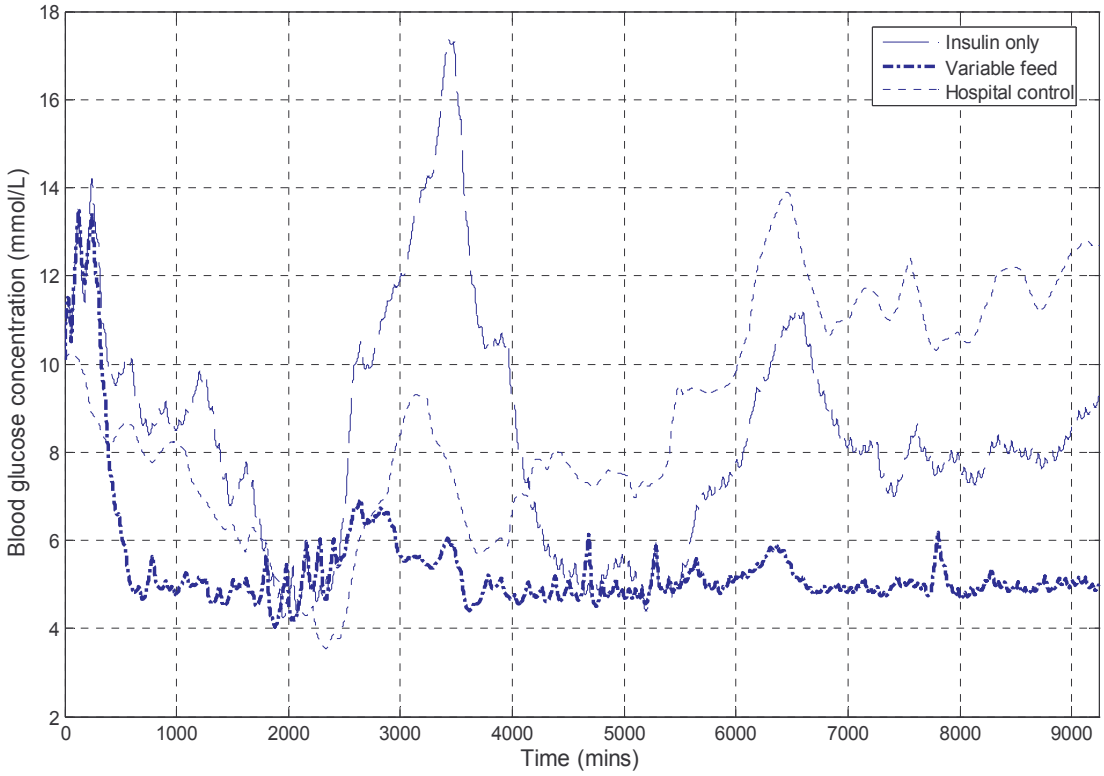

Figure 4: Patient 87 blood glucose level virtual trial results

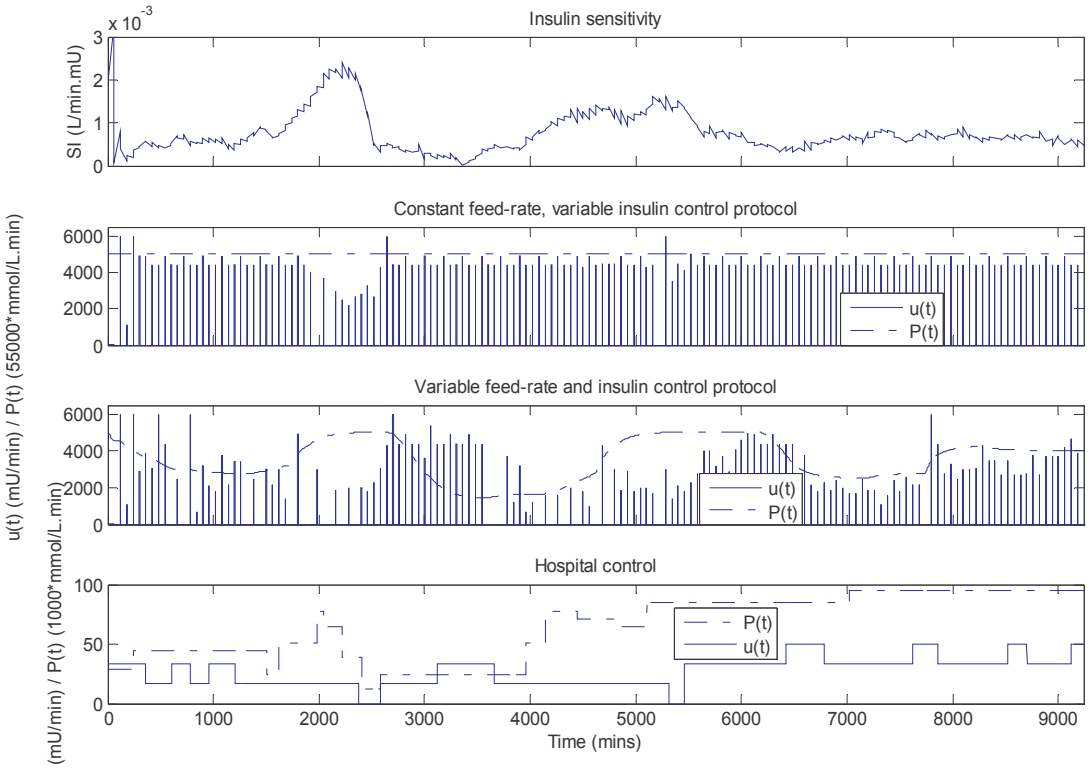

Figure 5: Patient 2 insulin sensitivity with corresponding control input virtual trial results

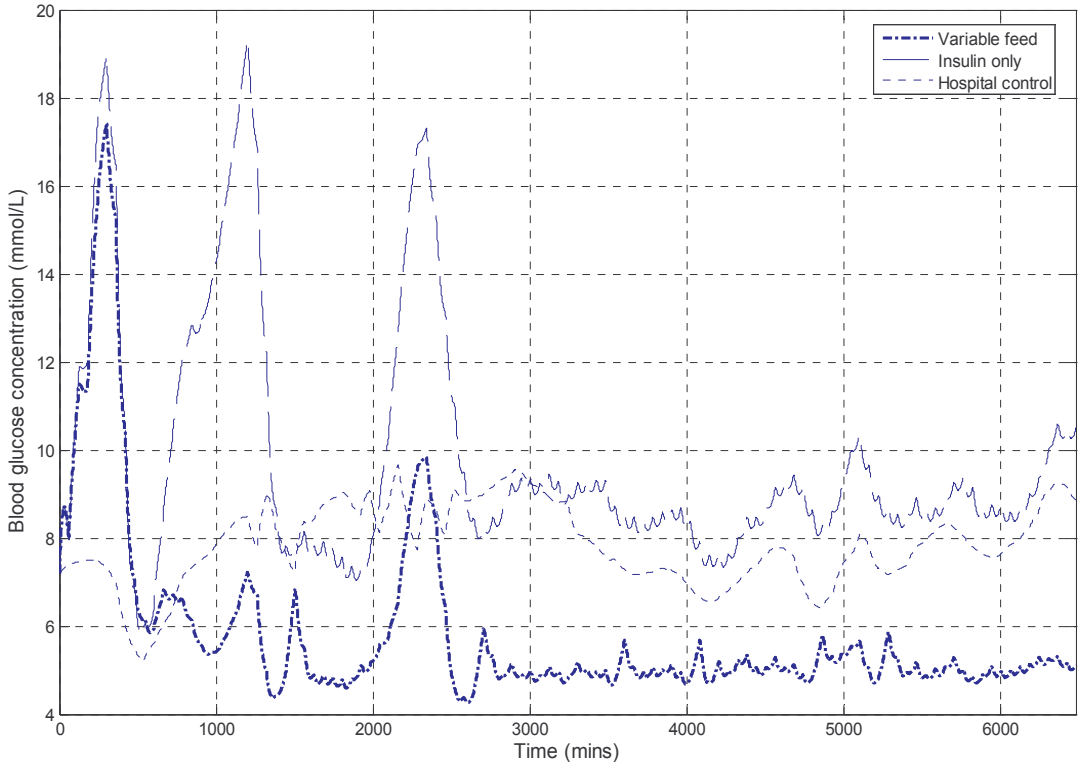

Figure 6: Patient 2 blood glucose level virtual trial results

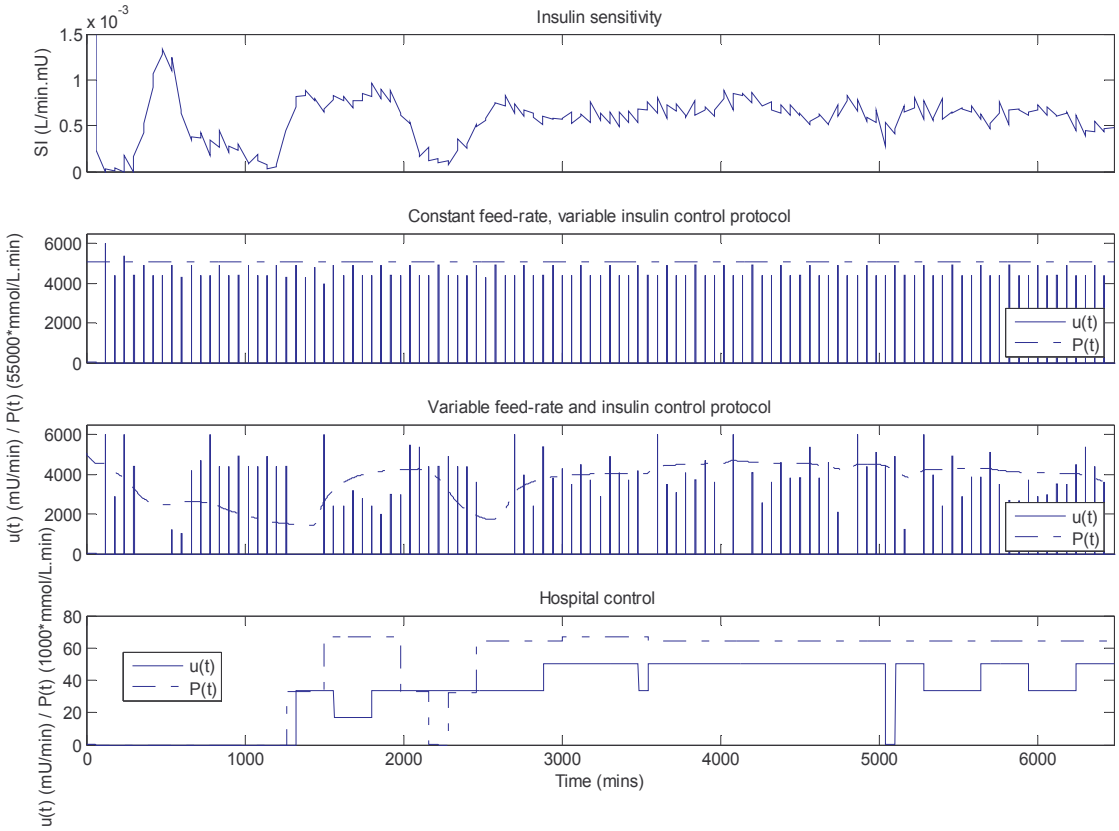

Figure 7: Patient 2 insulin sensitivity with corresponding control input virtual trial results

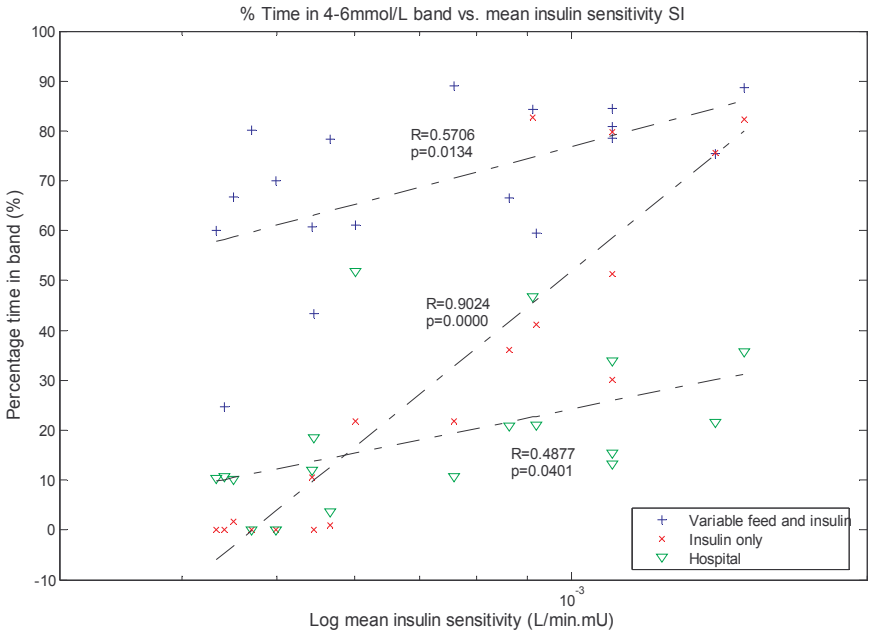

Figure 8: Percentage time in the 4-6mmol/L band versus the mean insulin sensitivity for the variable feed and insulin, insulin-only (with constant feed rate) and hospital control protocols

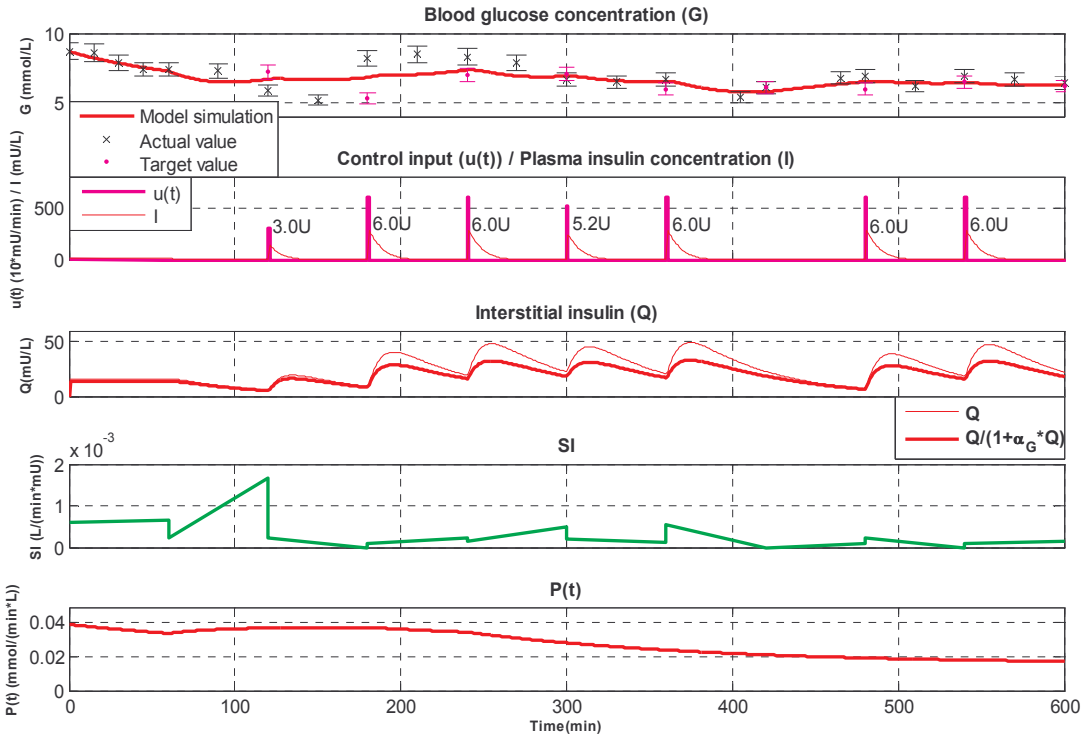

Figure 9: Patient A trial progression

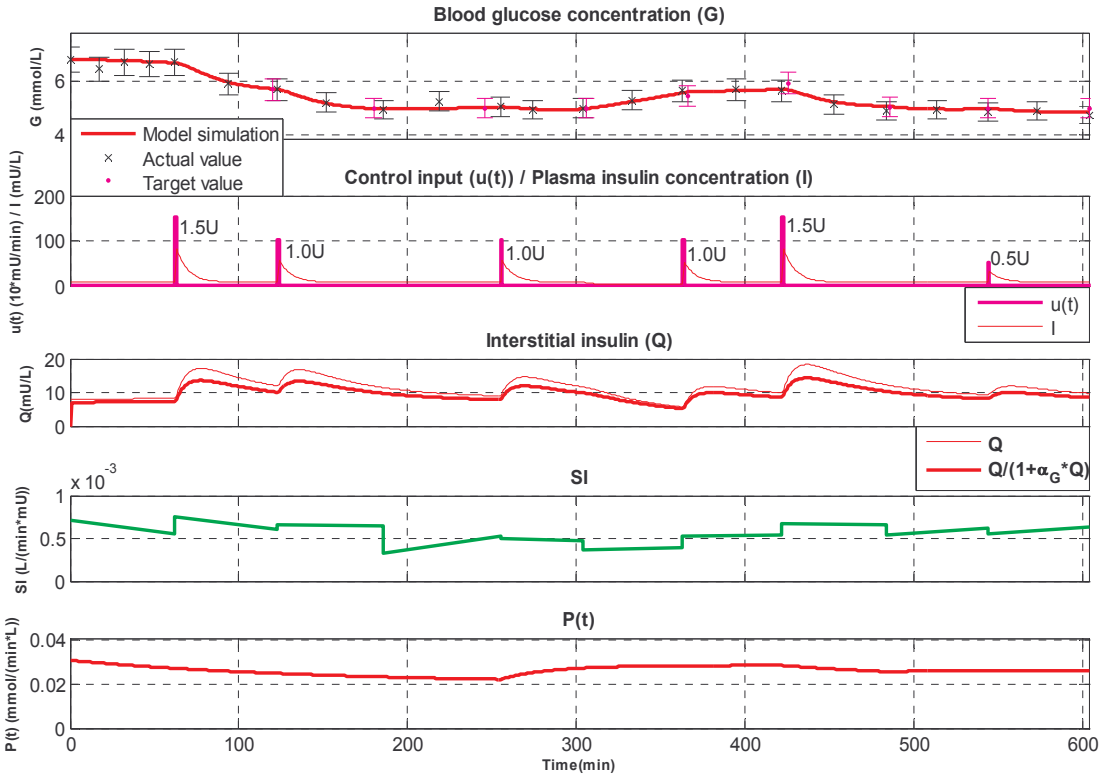

Figure 10: Patient B trial progression

TABLES

Table 1: Long-term virtual trial patient cohort

Patient number	Medical subgroup	Apache II score	Age	Sex	Mortality	Diabetes
1	Sepsis	Unknown	56	M		Type 2
2	Sepsis	Unknown	64	M		
24	Other medical	25	47	M	Y	Type 1
87	Other medical	26	62	F		
130	Trauma	11	21	M		Type 1
229	Cardiac	15	73	F		
289	Cardiac	18	70	M		
468	General surgical	32	76	M		
484	Other medical	34	30	F		
486	General surgical	22	76	F		Type 2
519	General surgical	29	69	M		Type 2
554	Other medical	26	20	F		Type 1
666	Cardiac	8	44	F		Type 2
847	Other medical	17	67	F		
1016	General surgical	20	37	F		Type 2
1025	Pulmonary	36	48	M		Type 2
1090	General surgical	Unknown	37	F		
1099	Pulmonary	Unknown	24	M	Y	
1125	Other medical	Unknown	72	F	Y	

Table 2: Virtual trial metrics results for the variable feed and insulin, insulin-only (with constant feed rate) and hospital control protocols

		Percentage of time in 4-6mmol/L band (%)			Percentage of time below 4-6mmol/L band (%)			Percentage of time above 4-6mmol/L band (%)		
Controller Type		Variable feed and insulin	Constant feed-rate, variable insulin	Hospital	Variable feed and insulin	Constant feed-rate, variable insulin	Hospital	Variable feed and insulin	Constant feed-rate, variable insulin	Hospital
Patient No.	1	66.8	1.6	10.2	0.9	0.0	0.7	32.3	98.4	89.1
	2	**78.4**	**0.9**	**3.6**	**0.0**	**0.0**	**0.0**	**21.6**	**99.1**	**96.4**
	24	80.1	0.0	0.0	0.0	0.0	0.0	19.9	100.0	100.0
	87	**89.1**	**21.8**	**10.7**	**0.0**	**0.0**	**2.6**	**10.9**	**78.2**	**86.8**
	130	60.1	0.0	10.3	0.0	0.0	0.0	40.0	100.0	89.7
	229	84.6	30.2	15.5	1.7	0.0	0.0	13.8	69.8	84.5
	289	80.8	79.8	13.2	0.8	0.0	0.0	18.4	20.3	86.8
	468	43.4	0.0	18.5	0.0	0.0	0.0	56.6	100.0	81.6
	484	70.0	0.0	0.0	0.0	0.0	0.0	30.0	100.0	100.0
	486	60.7	10.6	12.0	3.6	0.0	0.0	35.7	89.4	88.0
	519	78.6	51.4	33.9	2.3	0.0	3.4	19.1	48.7	62.7
	554	66.5	36.1	20.9	3.9	0.0	16.9	29.6	63.9	62.3
	666	35.7	0.0	74.9	0.0	0.0	8.9	64.3	100.0	16.3
	847	75.5	75.7	21.7	2.3	0.0	0.0	22.3	24.3	78.3
	1016	24.7	0.0	10.7	0.0	0.0	0.0	75.3	100.0	89.3
	1025	59.5	41.3	21.0	4.2	0.0	0.7	36.3	58.8	78.3
	1090	84.4	82.6	46.8	0.0	0.0	53.3	15.6	17.4	0.0
	1099	88.6	82.4	35.8	0.0	1.2	0.0	11.4	16.4	64.2
	1125	61.0	21.8	51.8	2.8	0.0	8.6	36.1	78.2	39.5
Mean		**67.8**	**28.2**	**21.7**	**1.2**	**0.1**	**5.0**	**31.0**	**71.7**	**73.4**
S. D.		**17.9**	**31.8**	**19.3**	**1.5**	**0.3**	**12.5**	**17.9**	**31.9**	**27.5**

Table 3: Total insulin administered, total glucose administered and the percentage of the total glucose administered out of the maximum glucose feed (1000kcal/day) for the variable feed and insulin, insulin-only (with constant feed rate) and hospital control protocols

		Total insulin administered (U)			Total glucose administered (g)			Average percentage of maximum glucose (1000kcal/day) administered (%)	
Controller Type		With feed variability	Insulin bolus-only	Hospital	With feed variability	Insulin bolus-only	Hospital	With feed variability	Hospital
Patient No.	1	1488	2042	1125	2720	5355	2606	51	49
	2	370	486	213	931	1285	672	72	52
	24	127	215	183	305	583	577	52	99
	87	411	667	248	1284	1833	1286	70	70
	130	97	143	111	188	393	143	48	36
	229	567	1032	232	2564	2868	1940	89	68
	289	88	108	42	440	476	312	92	65
	468	58	77	41	176	238	264	74	111
	484	125	172	200	312	476	492	66	103
	486	123	162	82	307	464	296	66	64
	519	706	1234	221	2836	3499	1856	81	53
	554	134	198	90	508	643	348	79	54
	666	150	169	61	203	464	62	44	13
	847	60	109	41	426	441	407	97	92
	1016	159	166	62	239	464	166	51	36
	1025	101	163	59	412	476	370	86	78
	1090	99	135	39	415	464	125	89	27
	1099	64	77	51	440	464	480	95	103
	1125	104	156	41	287	476	141	60	30
Mean		**264.7**	**395.1**	**165.3**	**789.2**	**1124.4**	**660.2**	**71.8**	**63.4**
S. D.		**347.9**	**515.9**	**244.6**	**894.5**	**1359.7**	**722.5**	**17.3**	**28.7**

Table 4: Mean blood glucose achieved and calculated insulin sensitivity for the variable feed and insulin, insulin-only (with constant feed rate) and hospital control protocols

		Mean Blood Glucose			Insulin sensitivity (L/min.mU)		
Controller Type		Variable feed and insulin	Constant feed-rate, variable insulin	Hospital	Mean	S. D.	Range
Patient No.	1	6.0	12.1	9.3	4.52E-04	2.65E-04	1.90E-03
	2	5.9	9.8	7.8	5.67E-04	2.39E-04	1.20E-03
	24	6.6	12.4	12.2	4.71E-04	1.59E-04	8.38E-04
	87	5.4	8.4	8.8	7.59E-04	4.42E-04	2.20E-03
	130	7.0	13.2	11.2	4.34E-04	2.77E-04	1.10E-03
	229	5.4	7.7	7.5	1.10E-03	5.49E-04	2.40E-03
	289	5.3	5.5	6.8	1.10E-03	3.73E-04	1.60E-03
	468	8.5	10.4	7.4	5.46E-04	2.58E-04	8.92E-04
	484	7.5	12.3	11.5	4.99E-04	1.32E-04	4.98E-04
	486	6.5	9.4	8.9	5.43E-04	3.10E-04	1.20E-03
	519	5.6	7.8	6.3	1.10E-03	5.93E-04	2.50E-03
	554	6.0	7.6	6.9	8.63E-04	5.35E-04	2.00E-03
	666	7.2	12.4	5.3	3.25E-04	1.70E-04	6.63E-04
	847	6.2	6.2	7.3	1.40E-03	4.78E-04	1.70E-03
	1016	7.5	9.4	7.2	4.42E-04	2.06E-04	7.55E-04
	1025	6.4	7.9	8.0	9.19E-04	4.34E-04	2.20E-03
	1090	5.2	5.3	3.9	9.12E-04	2.09E-04	8.21E-04
	1099	5.3	5.5	6.5	1.50E-03	4.07E-04	1.60E-03
	1125	5.9	7.3	5.4	6.01E-04	3.54E-04	1.30E-03
	Mean	6.3	9.0	7.8	7.65E-04	3.36E-04	1.44E-03
	S. D.	0.9	2.6	2.2	3.47E-04	1.41E-04	6.28E-04

Table 5: Trial 2 effectiveness of the variable feed and insulin control algorithm represented by accuracy of target acquisition

Time (mins)	Target glucose (mmol/L)	Achieved glucose (mmol/L)	Error (%) (abs)
120	7.22	5.90	18.28 (1.32)
180	5.32	8.20	-54.14 (-2.88)
240	6.97	8.40	-20.52 (-1.43)
300	7.06	6.70	5.1 (0.36)
360	6.00	6.70	-11.67 (-0.7)
420	6.10	6.10	0 (0)
480	6.00	6.90	-15 (-0.9)
540	6.49	6.95	-7.09 (-0.46)
600	6.20	6.45	-4.03 (-0.25)

Table 6: Trial 5 effectiveness of the variable feed and insulin control algorithm represented by accuracy of target acquisition

Time (mins)	Target glucose (mmol/L)	Achieved glucose (mmol/L)	Error (%) (abs)
120	5.69	5.70	-0.18 (-0.01)
180	5.00	4.95	1.00 (0.05)
240	5.00	5.05	-1 (-0.05)
300	5.00	5.00	0 (0)
360	5.46	5.65	-3.48 (-0.19)
420	5.93	5.65	4.72 (0.28)
480	5.04	4.90	2.78 (0.14)
540	5.00	4.85	3.00 (0.15)
600	5.00	4.75	5.00 (0.25)